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Biosurface and Biotribology 1 (2015) 229–248
www.elsevier.com/locate/bsbt

Realising the potential of graphene-based materials for biosurfaces – A future perspective

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Received 25 May 2015; accepted 28 October 2015

Abstract

Recently, the promising mechanical, tribological and biomedical properties of graphene and its derivatives (mainly graphene oxide and reduced graphene oxide) and graphene-reinforced nanocomposites have attracted great attention of tribologists, biomedical researchers and clinical doctors. In this paper, the tribology and biocompatibility of graphene-based materials are reviewed first to serve as a basis for the succeeding discussion. Then the current status of biosurface engineering with graphene-based materials and graphene-reinforced nanocomposites is overviewed. Finally, the potential of graphene-based materials for biosurfaces is discussed and the future directions are recommended.

Keywords: Graphene; Graphene oxide; Tribology; Biocompatibility; Biosurface

Contents

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Peer review under responsibility of Southwest Jiaotong University.

http://dx.doi.org/10.1016/j.bsbt.2015.10.004

1. Introduction

Graphene is a one-atom thick, honeycomb-like sheet of sp^2-hybridised carbon atoms with a conjugated system of overlapping pi electrons. As a typical two-dimensional material, graphene is the building block for other carbon structures such as 0D fullerene, 1D carbon nanotube (CNT) and 3D graphite [1]. By introducing proper defects and/or functional groups to the basal plane, graphene can be used as backbone for many derivatives such as graphene oxide (GO), graphane, fluorographene and graphene-based nanocomposites, which facilitates tremendous applications of graphene in various fields [2,3].

Notwithstanding the fact that the theoretical studies of graphene can date back to 1940s [4–6] and the attempts to obtain carbon monolayer has never stopped since decades ago [7–12], it was not until 2004 that pristine, monolayer graphene of high quality was isolated using the simple Scotch-tape method by Novoselov et al. [13,14]. Their "ground-breaking experiment" has not only contradicted the long-standing presumption that strict 2D crystals could not exist [15,16] but also uncovered some astonishing properties of graphene which has stimulated the field of graphene [1,17].

The unique structure enables graphene many distinctive properties and promising applications. Graphene is a zero band gap semiconductor with giant carrier mobility of up to 200,000 $cm^2/(V\,S)$ and proved quantum Hall effect [13,14,18,19]. The light transmittance of monolayer graphene can be as high as 97.7% [17], making graphene a hot candidate for electronic materials such as field emission transistors [20], transparent and flexible electrodes/films [21–24], window materials for solar cells [25,26] and gas/chemical sensors [27]. The high aspect ratio and strong sp^2 C–C bonds of graphene make it not only the thinnest and ultralight material, but also the strongest material ever discovered to date. The intrinsic strength and Young's modulus of a single layer graphene have been reported to be 130 GPa and 1.0 TPa, respectively, by either AFM measurement [28] or theoretical simulation [29]. It was estimated that graphene is 100 times stronger than the best steel ever, provided that they have an identical thickness. The excellent mechanical properties have attracted more and more research interest in using graphene and its derivatives as nano fillers for composites [30–33]. A thermal conductivity of 5000 W/(m K) has also been reported for graphene [34], which is 10 times higher than that of Cu and superior to carbon nanotubes (CNTs) and diamond.

Chemically derived graphene (CDG), mainly referring to graphene oxide (GO) or reduced graphene oxide (rGO), has been intensively studied due to its straight forward, scalable and low-cost synthesis [35–37] although mechanical exfoliation or chemical vapour deposition (CVD) could produce graphene with relatively less defects. As the result of chemical oxidation and exfoliation of graphite, a graphene structure with various functional groups such as hydroxyl, epoxide and carboxyl groups, is formed [38]. Although these oxygen functional groups disrupt the pristine 2D structure of graphene and deteriorate some of its fantastic properties, they provide a box of tools for further functionalization of graphene [3,26], and thus greatly broaden its applications. For biomedical

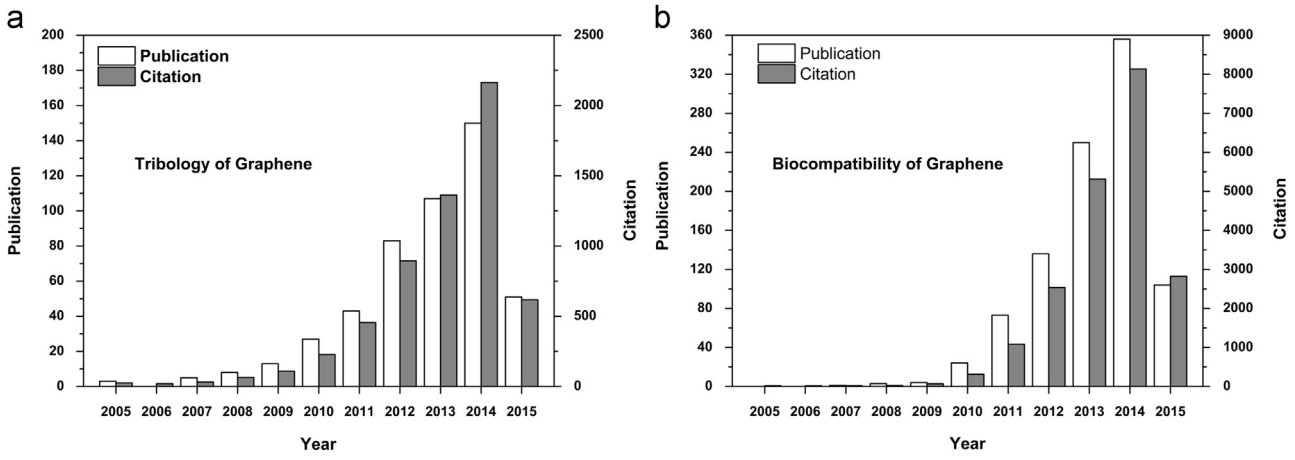

Fig. 1. Publication and citation statistics for Topics (a) Tribolo*/Friction/Wear+Graphene and (b) Biocompatib*+Graphene, respectively in the past 10 years. Data retrieved from Web of Science™ on 16th April 2015.

applications, CDG even displays better performance in terms of biocompatibility than pristine graphene.

Recently, the desirable tribological properties of graphene and its derivatives (mainly GO and rGO) especially low-friction and solid lubrication have received increasing attention of tribologists (Fig. 1a). Therefore, graphene and its derivatives could be ideal coating materials for surface engineering. The biocompatibility of graphene has also been investigated intensively either in vitro or in vivo (Fig. 1b). It has been reported that due to its unique structure and properties graphene and its derivatives (mainly GO and rGO) not only show good bioactivity but also could induce specific host responses, although there exist some disputes in the cytotoxicity of graphene, especially for its long-term health impact. Graphene and its derivatives have shown the potential for various biomedical applications such as bio-sensing and imaging, drug delivery and tissue engineering.

Given the remarkable mechanical and tribological properties in conjunction with its recently revealed good biocompatibility and attractive bioactivity, graphene-based materials could have great potential in biotribological applications. However, to our knowledge the biotribology of graphene has not been overviewed. In this paper, the tribology and biocompatibility of graphene-based materials are described first to serve as the basis for the succeeding discussion and then the current status of the bio-tribological applications (such as orthopaedic and orthodontic devices) of graphene-based materials is overviewed. Finally, the potential of graphene-based materials in bio-tribological applications is discussed and the future directions are recommended.

2. Tribology of graphene

2.1. Nano/micro-scale tribology

Given the nanomaterial nature of graphene, the tribological behaviour of graphene and its derivatives has been studied mainly in nano/micro-scale using atomic force microscopy (AFM), friction force microscopy (FFM), computer simulation and theoretical analysis.

2.1.1. Frictional behaviour of pristine graphene

One of the earliest studies in this field was reported by Lee et al. in 2009 [39], in which the frictional behaviour of mechanically exfoliated graphene with varying layer numbers was investigated using AFM and FFM techniques. It was found that the frictional force decreased monotonically as the number of graphene layers increased and eventually reached that of bulk graphite [39]. Similar results were reported by Filleter et al. [40], who found that for graphene grown epitaxially on SiC, the friction of monolayer was twice that of bilayer.

Earlier TEM observation has revealed that to achieve thermal stability graphene monolayer is not perfectly flat but has intrinsic ripples [41]. Thus a "rippling-rug" mechanism was proposed [39,42]: the out-of-plane ripples and puckering increase the contact area between the tip and the graphene sheet (Fig. 2), thus increasing friction. Further experiments [43] and finite element modelling (FEM) [42] also demonstrated that this rippling-rug or puckering effect is more evident for monolayer graphene which is weakly bonded to the substrate or freely suspended; on the other hand this effect will be suppressed if graphene is strongly bonded to the substrate or the graphene sheet is thick and stiff. This out-of-plane deformation mechanism has been supported by molecular dynamics (MD) simulations [44,45]. In addition, Filleter et al. [40,46] concluded from angle-resolved-photoemission spectroscopy (ARPES) results that the friction difference between mono- and bi-layer graphene could arise from their different energy dissipation behaviour.

It is well known that bulk graphite shows great lubricity due to interlayer shear, which is the same case for graphene sheets composed of more than one layer. The friction between graphene layers depends mainly on the interlayer interaction including interlayer distance and stacking state [47]. For bulk graphite, the layers are stacked tightly in an ABAB registry (so called commensurate stacking) with a layer spacing of

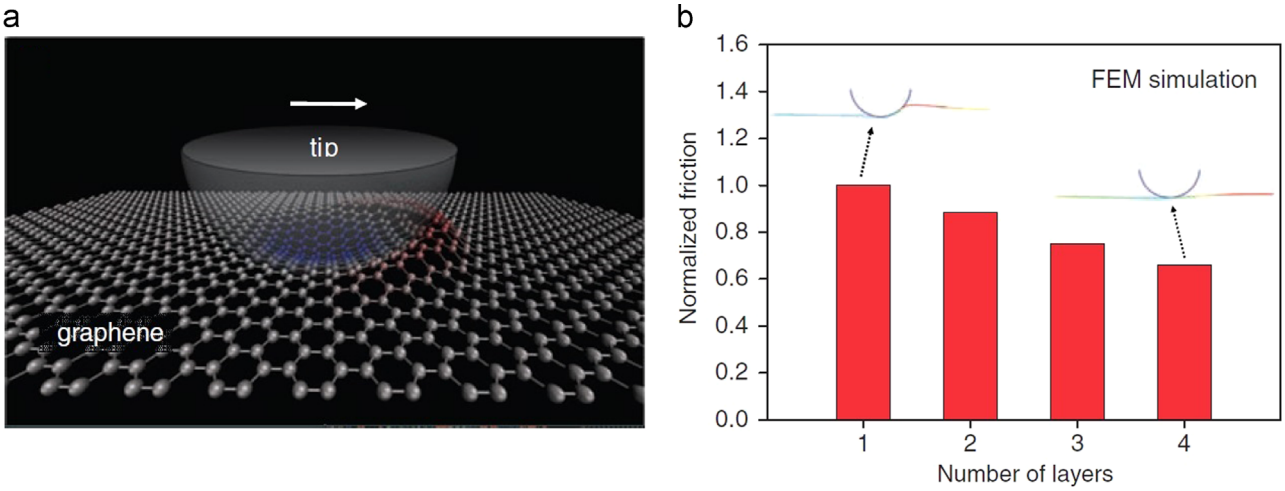

Fig. 2. (a) Schematic of puckering effect of a graphene sheet under an AFM tip and (b) the layer dependence of friction based on FEM simulation [42].

0.34 nm. Incommensurate contact results in a reduction of energy required for interlayer sliding, thus decreasing the interlayer friction, even leading to superlubricity [47].

It was reported by Li et al. [43] that the trend of decreasing friction force with respect to graphene thickness was absent in the case of mica substrate, where the graphene is strongly adhered to the mica sheet. This is mainly because the surface of freshly cleaved mica is atomically flat and graphene always follows the contour of the underlying substrate [48]. The suppression of out-of-plane deformation (such as ripples) reduces the friction. This is echoed by Cho et al. [49] who investigated the friction of graphene on various substrates, including SiO_2, h-BN, bulk-like graphene (graphite) and mica by FFM. They found that graphene on SiO_2 substrate showed the same friction-thickness dependence as Lee et al. reported [39,42]. However, the friction of graphene on atomically flat substrates, such as h-BN and bulk-like graphene, was not only as low as that of bulk graphite but also independent on the number of graphene layers. Marchetto et al. [50] investigated the friction and wear of single layer graphene epitaxially grown on SiC at microscale using multi-asperity FFM using Ruby sphere tips under the applied normal load varied from 0.1 to 1.0 mN. A super low initial friction coefficient of 0.02 was found, and the value evolved to be 0.08 after a hundred cycles of reciprocating sliding. The remarkable lubricating behaviour was attributed to the hard SiC substrate and strong interface bonding that prevented the out-of-plane deformation, thus reducing the contact area, which in turn reduced the friction.

Transfer of graphene film onto different substrates is very necessary for practical tribological applications, especially in the case of CVD-grown graphene where only a very limited number of metals, such as Ni and Cu, can be used for graphene growing. However, the deformation and defects caused by the transfer process and the roughness of the target substrate will inherently increase friction. For example, the friction coefficient of graphene films grown on Ni foil by CVD was 0.03 [51] which is remarkably low and consistent with the results of Shin et al. [52]; in contrast, however, after being transferred on to silicon dioxide substrate the friction coefficient raised up to 0.12, close to that for bulk graphite (Fig. 3 [51]). The reason for this increase was contributed to the inadequate adhesion between the transferred graphene film and the substrate, which is partially because of the contaminations and wrinkles caused by the transfer. Even so, transferred CVD-grown graphene can still impressively reduced the friction [51,53] and improved the mechanical properties [54] of the target substrate.

Although the interactions between the AFM tip and graphene are so complex that the effect of some related factors, such as normal force, sliding velocity and tip size, on the nano/micro tribology of graphene remains uncertain [55,56], it follows from the above discussion that graphene possesses very low friction provided it is firmly bonded on atomically flat substrates to avoid out-of-plane ripples and puckering.

2.1.2. *Frictional behaviour of doped graphene*

Considering that most graphene products always contain defects, deformations and functional groups in graphene lattice, it is understandable that the reported tribological characteristics of graphene are variable and usually far from the theoretically expected values. For instance, it has been reported by Shin et al. [52] that the friction of both mechanically exfoliated and epitaxially-grown graphene increased after oxygen plasma treatment, which introduced defects in graphene structure by ion bombardment. The plasma treatment induced defects increased the polarity of graphene surface and the attractive van der Waals forces between the AFM tip and graphene layer, thus resulting in an increase of friction. In the tribological simulations by Bonelli et al. [57], it was shown that graphene with a larger flake size experienced lower friction, even superlubricity, compared with smaller flakes. This is because graphene edges can be seen as structural defects, and larger graphene flakes are supposed to have less such defects due to their higher area-to-edge ratios. Similar influence of defects on the friction of graphene has also been reported by Won et al. [58].

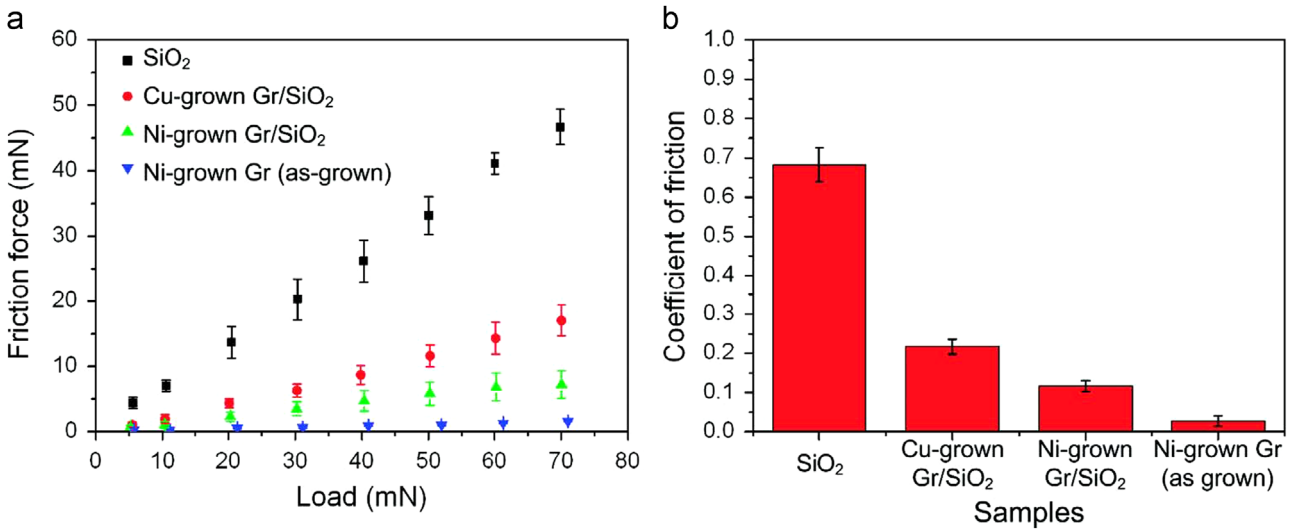

Fig. 3. (a) Friction force as a function of load and (b) coefficient of friction for graphene samples. Gr: graphene [51].

Functionalization of graphene has attracted increasing research interest in recent years [3,59], and the modification of the surface chemistry of graphene greatly enriches the chemical activities of graphene and hence encourages its real applications. Graphene can be modified by breaking the C=C bond and introducing other elements such as hydrogen or fluorine, ending up with graphane or fluorographene, respectively. Otherwise, oxygen functional groups, such as hydroxyl (–OH), carbonyl (–C=O) and carboxyl (–COOH), can be grafted in plane or on the edge to form so-called GO and rGO. Ko and co-workers [60,61] investigated the nanotribological behaviour of fluorinated, hydrogenated and oxidised graphenes by FFM measurements and density functional theory (DFT) calculations. They found that the nanoscale friction increased by 2, 6 and 7 times for hydrogenated, fluorinated and oxidised graphenes, respectively, compared to that of pristine graphene.

Several friction and wear mechanisms for functionalised graphene have also been reported [62–65]. Li et al. [62] concluded from their experiments and simulations on fluorinated graphene that the dramatic friction increase is due to increased energy corrugation, as demonstrated in Fig. 4, which is probably caused by the strong local charge concentrated at fluorine sites. Fessler and co-workers [63] studied plasma-hydrogenated graphene on SiO_2 substrate using FFM and observed a similar increase of friction for hydrogenated graphene, compared to pristine graphene. Berman et al. [64] conducted nano-tribological tests on multilayer graphene and graphene oxide using AFM. It was shown that the quality of multilayer graphene plays an important role in the friction reduction. High-purity graphene grown by CVD showed significantly lower friction than highly oriented pyrolytic graphite (HOPG) and oxidised graphene.

In a report by Peng and co-workers [65], mechanically exfoliated multilayer graphene (MEMG), multilayer graphene oxide (MGO) and multilayer reduced graphene oxide (MRGO) were deposited on SiO_2 substrate and their nanotribological properties were investigated by AFM in ambient conditions. All three types of graphene layers exhibited reduced friction with respect to bare SiO_2 substrate. The friction value is reduced in the order of MEMG, MRGO and MGO [65]. The MEMG holds the lowest friction or the best lubricity due to its perfect planar lattice and hydrophobic nature. In contrast the oxygen functional groups lead to a hydrophilic surface especially for MGO, thus increasing the friction. More recent work by Chen and Filleter [66] has further confirmed that when applied as solid lubricants between a sliding contact of a Si tip and a SiO_2 substrate few layer graphene and GO can reduce friction by about 6 and 2 times respectively as compared to the unlubricated contact; in addition, the wear of GO decreased with increasing its C/O ratio and it is possible to achieve graphene-like tribological properties by tailoring the structure of GO. This effect should be taken into consideration for tribological applications, for example implant materials where graphene is usually functionalised using various oxygen containing groups or molecules but low friction and wear are still needed.

It is worth noting that in some published work the friction of bulk graphite was determined to be lower than that of graphene (less than 5 layers) [39,42,43,49,55], while in contrary some other authors reported that bulk graphite showed friction higher than few-layer graphene [40,46,50–52,64]. This difference can be attributed to the effect of various graphite sources and testing environments, the quality and purity of graphene [64] and the bonding between the CVD-grown graphene and the substrate [51].

2.2. Macro-scale tribology of graphene-based materials

While the nano/micro scale studies have provided many insights towards the mechanism of nanotribology of graphene and nanofriction in particular, it is essential to investigate the tribology of graphene and graphene-based materials in macro scale using conventional reciprocating or unidirectional sliding tribometers to provide more relevant information for real applications. Generally, the macro-scale friction and wear properties of graphene have been studied in forms of graphene-based coatings, graphene-reinforced composites and graphene-based lubricant additives (which is not reviewed in this paper).

2.2.1. Graphene-based surface coatings

Berman et al. from Argonne National Laboratory in the USA have pioneered the attempts at using graphene as a solid lubricating coating on metallic substrates [67–71]. In their work [68,69], solution-processed graphene (SPG) prepared by chemical exfoliation of graphene was dispersed in ethanol and then spread on highly polished surfaces of 440C stainless steel. After evaporating the ethanol in dry nitrogen, a graphene

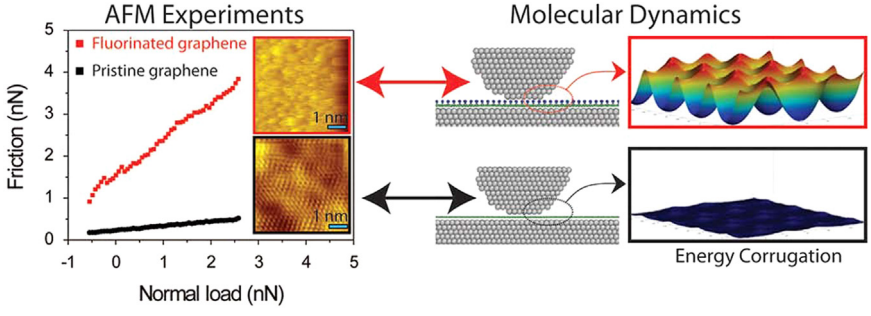

Fig. 4. Friction as a function of normal load for pristine (black) and fluorinated (red) graphenes and their AFM friction images. A clear stick-slip motion is demonstrated on pristine graphene. Contour maps of the tip-sample potential energy for the two samples are provided [62].

coating of 2–3 layers was formed on the steel surface. It was revealed by SEM and Raman analysis that the graphene coating was non-continuous with merely 25% coverage. The tribological behaviour of the graphene coated steel against 440C steel balls (9.5 mm in diameter) in both humid air (30% RH) and dry nitrogen was assessed using a ball-on-disk tribometer under a normal load of 1–5 N at a sliding speed of 9 cm/s. The results have demonstrated that the few-layer graphene film exhibited excellent lubricating ability regardless of testing environments. In both humid air and dry nitrogen environment the graphene coated steel demonstrated stable and low friction (0.15–0.20). The wear rates were found to be reduced as much as 4 and 2 orders of magnitude in humid air and dry nitrogen, respectively. This is in contrast to graphite, which lubricates well in humid environment but is much less effective in dry environment [67].

In another work [70] Berman and co-workers conducted the same tribological tests in hydrogen and nitrogen environments to study the effect of different atmospheres on the tribology of graphene. Apart from the few-layer graphene film employed in their previous study, single-layer graphene prepared by CVD on copper foil and then transferred onto 440C steel was also used in this work. It was found that in hydrogen atmosphere while single layer graphene survived 6400 sliding cycles, the few-layer graphene (3–4 layers) lasted for up to 47,000 cycles. The wear rate was effectively reduced from about $1.5x10^{-9}$ for the steel-to-steel tribo-pair to $5x10^{-12}$ and $1x10^{-12}$ mm^3/N mm for single layer and multilayer graphene respectively. By contrary, when tested in nitrogen the single layer graphene lasted for no more than 500 cycles and the wear rate was rather high ($9x10^{-10}$ mm^3/N mm). Through MD simulation the authors associated the favourable tribological behaviour in the hydrogen case with the passivation effect of hydrogen. When graphene with defects is exposed to hydrogen gas, the hydrogen atoms tend to occupy and stabilise the defect sites, thus protecting the underlying graphene from severe damage and extending the wear life. However the simulation results suggested that this passivation effect is absent in the nitrogen case, therefore the graphene layer underwent a rapid disintegration.

To compare the lubricating features of graphene and graphene oxide, Berman et al. [67] tested the friction and wear of GO coated steel under the same conditions. Graphene oxide (GO) was shown to have low friction coefficient (~0.2) comparable to graphene in both nitrogen and humid environment. This is in contrast to the results from nano/micro scale studies [60,64,65] that GO normally shows a higher friction than graphene (see Section 2.1). However the wear rate of GO is 1–2 orders of magnitude larger than that of graphene. It was argued from a tribo-corrosion view that although the layered structure of GO enables the easy shear and thus reduces the friction, the oxygen groups in GO can lead to oxidation and corrosion of the substrate, which in turn deteriorate the wear resistance. Table 1 compares the tribological behaviour of steel, graphite, graphene and graphene oxide sliding against a steel surface in a range of environments.

Table 1
Tribological behaviours of graphene, graphene oxide or graphite coated steel against another steel surface in humid and dry environments. SPG/SPGO: solution processed graphene/graphene oxide [67].

Tribo-pair	Environment	Friction	Wear rate ($\times 10^{-9}$ mm^3/N m)
Steel vs Steel	Humid air	1	18,000
	Nitrogen	0.9	1310
SPG-steel vs Steel	SPG drops/ Humid air	0.15	3.01
	Nitrogen	0.15	2.54
SPGO-steel vs Steel	Water/Humid air	0.17	65.1
	Nitrogen	0.16	208
Graphite-steel vs Steel	Humid air	0.17	49.4
	Nitrogen	0.8	507

Although it has been shown clearly that pristine graphene is superior to any modified graphene in terms of both mechanical and tribological properties, to the best of our knowledge the reports by Berman and co-workers are the only publications available that have employed pristine graphene as a solid lubricant at macro scale. The reason is the difficulty to produce pristine graphene in large scale due to the low yield and complex transfer process for methods such as mechanical exfoliation, chemical defect-free exfoliation and CVD [2]. Therefore, instead of pristine graphene the majority of the macro-scale tribological studies on graphene have used graphene oxide (GO) or reduced graphene oxide (rGO), which hold advantages such as scalable production, improved and stable dispersion in various solvents [72] and versatile deposition methods [26]. Moreover, the oxygen groups in GO and rGO enable further functionalization by numerous ways [3], beneficially broadening their applications.

For example, Liang et al. [73] reported that graphene oxide film could serve as a promising solid lubricant for Micro/nanoelectromechanical systems (MEMS/NEMS). The GO film was fabricated directly on silicon wafer using a green and simple electrophoretic deposition (EPD) technique. The results of tribological tests showed that the friction coefficient and wear rate of the GO coated silicon wafer were reduced to 1/6 and 1/24 of its original values, respectively. This indicates that due to its excellent lubricity GO alone has the potential as a lubricating coating. Nonetheless, the normal load used in this work was only 400 mN and further tests under medium-to-high loads should be conducted to evaluate the durability, adhesion and load bearing capacity of the EPD deposited GO coating.

The adhesion of the graphene-based coating to the substrate can have a major influence on its tribological performance [49–51,64]. This is particularly important when dealing with macro scale fabrication of graphene-based coatings, since the roughness of material surface in real-life applications cannot be as low as ultraflat materials such as mica and h-BN, which are favourable in nanotribology of graphene. Therefore either graphene or the target substrate needs to be engineered to enhance the adhesion between them. Introducing bonding/transition layers is an important method that has been adapted

in literature [74–82]. For example, to address the adhesion issue, Ou et al. [74] introduced a 3-aminopropyl triethoxysilane (APTES) self-assembled monolayer (SAM) between the top rGO coating and the silicon substrate underneath. Due to the presence of free polar groups on the Si surface, the GO sheets were covalently bonded to the substrate via reactions between the amine groups of APTES and the epoxy and carboxyl groups in GO structure. Thus the adhesion between the GO coating and the substrate was enhanced effectively. The APTES bonding layer was also applied on titanium surfaces [80–82], which led to improved tribological properties. From the discussion above it can be concluded that by designing the structure of a graphene-based coating and tuning the chemistry of the coating surface, an improved and reliable lubricating performance could be expected from GO.

Due to many complex factors of the macroscopic world, such as high loads, complicated surface conditions, contaminations and quality and continuity of graphene in large scale, it is not strange that when zooming out to macro scale, the tribological properties of graphene are not always as perfect as observed in nano/micro scale. Although graphene-based coatings have shown great lubricity, more efforts still needed to be made to improve the reliability and durability of graphene-based coatings.

2.2.2. *Graphene-based composites*

In order to address the technological challenge of relatively weak bonding of graphene coatings on relatively large areas of materials surfaces (such as biomaterials), graphene-based composite coatings have been developed and their tribological properties explored [83–89].

Thangavel et al. [86] reported the structural and tribological properties of GO reinforced poly(vinylidene fluoride) (PVDF) nanocomposite thin films. After blending given content of PVDF powder with functionalised GO suspension, the mixture was spin cast on Si wafer and dried at 145 °C. The tribological properties of the composite coatings were evaluated using a reciprocating tribometer with a stainless steel counter ball under a load of 10 mN. The addition of GO in the polymer coating can reduce the friction and wear of both Si and PVDF. As expected an optimal GO content was observed, above which point both the friction coefficient and wear rate increased with GO content (Fig. 5 [86]). Likewise, Min et al. [87] found that the incorporation of GO into polyimide (PI) not only improved the mechanical and tribological properties but also enhanced the thermal stability of the composite. The effect of GO was believed to stem from the oxygen functional groups in GO which can help form a strong interface with the PI matrix. Thus the composites are toughened by GO sheets due to their intrinsic strength and high aspect ratio. Similarly Song et al. [88] reported that as a nanofiller for poly(ether ether ketone) (PEEK), GO was superior to multiwall carbon nanotube (MWCNT) in terms of the ability of reducing friction, extending wear life and improving the Young's modulus and tensile strength.

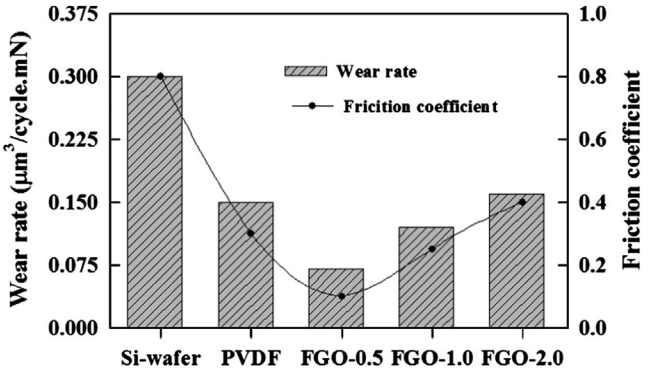

Fig. 5. Friction coefficients and wear rates of the PVDF-FGO thin films with different GO content [86].

Apart from graphene/polymer composite coatings, Li et al. [89] were able to fabricate graphene nanosheets (GNs) reinforced zirconia ceramic coating on Ti–6Al–4V substrate. To produce the composite coating. Graphene nanosheets of 5–20 nm and partially yttrium-stabilised zirconia spray powder were first mixed by ball milling, and then deposited on the Ti alloy using a plasma spraying technique. To enhance the adhesion a Ni–Cr bonding layer was applied. It was found that an addition of 1 wt% GNs reduced the wear rate by ~50%, and the friction coefficient was reduced from 0.27 to 0.19 when the normal load increased from 10 to 100 N. The improvement by GNs, especially under high load can be attributed to the formation of a continuous GN-reinforced transfer layer which effectively prevents the substrate from further damage, as demonstrated in Fig. 6. However, compared with GNs, graphite was less effective since the transfer layer was discontinuous. Due to its excellent tribological performance the zirconia/GNs composite coating could be potentially employed for biomedical applications.

Graphene and its derivatives as reinforcements for bulk composites have been studied intensively in recent years. Evidently GO instead of pristine graphene was the first choice for these studies, partially due to the oxygen groups in GO that enhance the interaction with composite matrix as discussed above and partially due to the relatively low cost and wide availability. However, most of these studies [30–33,90–94] have focused on the mechanical characteristics of the composites, and their tribological properties were rarely addressed [95–103].

To this end, Tai et al. [95] prepared GO/ultrahigh molecular weight polyethylene (UHMWPE) composites by hot pressing in 2012. It was found that both the hardness and wear resistance of the GO reinforced composites increased with the GO content up to 1.0 wt%. A transfer layer mechanism was proposed to explain the wear reduction, which is in agreement with other reports [89,101–103]. However, the friction increased slightly with increasing GO loading, consistent with reported phenomenon of CNT/UHMWPE composites [95]. Similar friction increase was also reported by Shen et al. [99,100] for their studies on GO/epoxy composites. The infusion of GO was found to increase the friction yet to reduce the wear significantly. In contrast, however, Lahiri et al. [96] have demonstrated that the friction coefficient of UHMWPE–matrix composites did not increase but go down with the reinforcement content if using graphene nanoplatelet

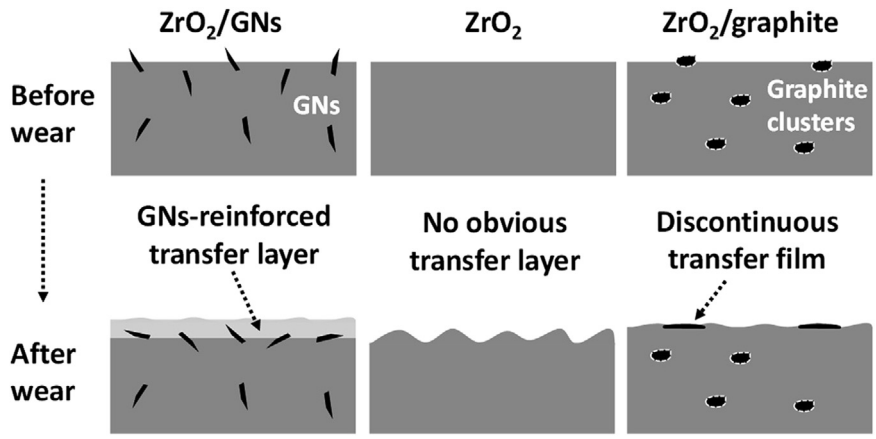

Fig. 6. Schematic of the formation of the transfer layer during wear test [89].

(GNP) instead of GO. It was argued to be due to the weak van der Waals bond and easy shear between graphene layers.

Kandanur et al. [98] reported the dramatic suppression of wear in GO incorporated polytetrafluoroethylene (PTFE) composites under a high normal load of 50 N. The wear rate was reduced by 10 fold with only 0.32 wt% GO fillers, and dramatically by 4000 fold with 10 wt% of GO platelets. Graphite reinforced PTFE, on the other hand, showed 10–30 times higher wear rate than in the graphene case, indicating the huge advantage of graphene as a lubricating nanofiller.

3. Biocompatibility of graphene

As discussed in the preceding section, graphene and its derivatives possess some very attractive tribological properties in terms of low-friction, high wear resistance and self-lubricating. Hence, there should be great potential for graphene and graphene-based materials to be used for engineering the surfaces of biomaterials for high-performance and long-life medical devices including various body implants. Therefore, the biocompatibility of graphene and its derivatives is a key factor to be considered for their potential biosurafce application.

3.1. Potential biological applications of graphene

The high aspect ratio, i.e. the high specific surface area of graphene layers enables graphene-based materials as platforms for various biological interactions. Molecules and functional groups can be either physically adsorbed via π–π stacking or covalently grafted on the graphene structure for different biomedical purposes. Particularly, surface functionalization of graphene, for example GO or rGO, is highly favourable for such applications, because a hydrophilic surface is highly desired in physiological environments for an enhanced biocompatibility. This is consistent with the case of CNTs, which are usually functionalised before biomedical applications and their biological performance shows a dependence on the degree of functionalization [104]. Moreover, the oxygen groups in GO and rGO can serve as interaction sites for further functionalization. In this context, GO and rGO are superior to pristine graphene. Apart from the tunable chemistry, the excellent mechanical, tribological as well as corrosion [93,105] properties of graphene-based materials allow their potential applications in implant and orthopaedic materials.

To date, graphene and its derivatives (mainly GO and rGO) have shown their potential for biomedical applications such as biosensors [106], drug delivery [107], antibacterial agent [108–110], tissue engineering [111] and orthopaedic implants [112], owing to their unique structures and properties [113–115].

3.2. Biocompatibility of graphene

Biocompatibility refers to “the ability of a material to perform with an appropriate host response in a specific application”. Host response refers to the reactions of blood, immune system and tissues to a biomaterial. A biocompatible material should not show perceptible cytotoxicity or cause any inflammation to human body [116]. For long-term contact any mutagenicity or carcinogenicity should not be observed. It is also important that a biomaterial should be able to induce “appropriate host response”. From a material point of view, moreover, the biomaterial should not degrade physically or chemically in human body after a long period.

3.2.1. Biocompatibility of graphene and its derivatives

At first it is worth making some general comparisons between pristine graphene, GO and rGO. It is known that CNTs without any functionalization can cause lesions in mice body [117], whereas functionalising CNTs with biomedical polymers such as PMMA, PCU, PLLA and PCS can improve the tissue regeneration and reduce inflammatory responses [104]. As a counterpart of CNTs, pristine graphene possesses a similar biocompatibility. The highly hydrophobic nature of pristine graphene makes it unstable and more likely to aggregate in liquid physiological environments and get trapped in some organs. It was reported [118] that graphene aggregations induced a high level of reactive oxygen species (ROS), which is liable for cell toxicity [113]. Moreover, the hydrophobic surface of graphene hinders the interaction with surrounding tissues, resulting in poor cell proliferation and

tissue regeneration. In contrast, GO is hydrophilic and exhibits much better dispersibility in various solvents [72] due to the presence of oxygen groups. For the same reason the protein adsorption, cell adhesion and proliferation on GO sheets can be improved [119], which is favourable for tissue engineering and implants. Therefore, graphene oxide instead of pristine graphene has been chosen for the majority of the work on the biomedical applications.

As partially reduced graphene oxide, the biocompatibility of rGO is expected to be lower than GO but higher than pristine graphene. The biocompatibility of rGO is therefore dependent on the oxygen content. Indeed, it has been reported by Liao et al. [118] that particle size, surface charge and oxygen content of graphene all have a large impact on the biological responses of red blood cells although GO is generally considered to be hemocompatiable [120]. It was found that aggregated graphene sheets showed the lowest hemolytic activity, i.e. fewest broken cells; while smaller GO size led to higher hemolytic activity, which can be attributed to the strong electrostatic interactions between negatively charged GO surface and positively charged lipids on the outer membrane of red blood cells. For simplicity, only GO and GO derivatives will be involved in the discussion in the following two sub-sections.

3.2.2. Cell toxicity

Although there remain some disputes on the cytotoxicity of graphene-based materials, the cytotoxicity of GO has been reported to be limited and dose-dependent. Wang et al. [121] investigated the biocompatibility of GO by culturing human fibroblast cells in GO containing environment and injecting GO into mice. It was shown that for human fibroblast cells GO did not exhibit cytotoxicity with a dose less thna 20 μg/ml but showed obvious toxicity when the GO dose exceeded 50 μg/ml. For mice the injection of GO did not exhibit obvious toxicity until the dose was increased to 0.4 mg, where chronic toxicity took place and cannot be cleaned by kidney. Similarly it was found [122] that GO showed a concentration-dependent toxicity on A549 human epithelial cells. Interestingly it was also observed that the toxicity occurred mainly at the initial stage and was not time-dependent. The toxicity mechanism was believed to be due to the physical damage caused by sharp GO sheets [122]. In their recent article Horvath et al. [123] reported that GO showed lower toxicity on epithelial cells compared with CNTs. In agreement with the observation in Ref. [122], the cytotoxicity occurred during the initial stage of exposure. The mechanism of toxicity in this case, however, was associated with the reactive oxygen species (ROS) generated by the interaction between GO and the cell surface. The lower toxicity of GO with respect to CNTs is consistent with the results by Yuan et al. [124].

In contrast, Chang et al. [125] examined the impact of GO on A549 cells and found that GO did not enter the cells and thus exhibited no toxicity. However a dose-dependent oxidative stress and ROS in cell was observed, which could be attributed to the strong catalytic activity of GO [113]. One of the rare *in vivo* investigations on the cytotoxicity of GO was provided by Yan et al. [126]. In their initial *in vitro* study, it was observed that the impact of GO on human retinal pigment epithelium cells (ARPE-19) was very little, but visible after long-time culturing. *In vivo* experiments were conducted by intravitally injecting GO into eye, and few change in eyeball was found, indicating that GO did not put toxicity on the cell proliferation.

It is worth noting that according to various studies the cytotoxicity of graphene was found to be varied on different cell lines. For example as can be seen above GO exhibited no or dose-dependent toxicity to A549 cells [122,123,125], human fibroblast cells [118,121], human hepatoma HepG2 cells [124] and ARPE-19 epithelial cells [126], but remarkable toxicity to red blood cells [118]. Interestingly, GO was reported to be cytotoxic to MCF-7 human breast cancer cells with a dose more than 60 μg/ml, resulting in decreasing cell viability, increasing ROS level and release of lactate dehydrogenase [127].

Many studies have shown that further functionalization of GO can improve its biocompatibility effectively [107,118,119,122,128]. Liu and colleagues [107,128] reported that nano GO functionalised by polyethylene glycol (PEG) exhibited no perceptible toxicity to many cell lines, such as U87MG, HCT-116 and OVCAR-3 even at a high GO dose up to 100 μg/ml. The *in vivo* experiment showed negligible accumulation of PEGylated GO in mice lung which could be excreted out without causing noticeable cytotoxicity over 3 months [128]. Liao et al. [118] found that the hemolytic activity caused by GO could be nearly eliminated by coating GO with chitosan. Hu et al. [122] showed that the toxicity of GO could be mitigated largely due to the presence of fetal bovine serum (FBS), a common component in cell culture medium.

3.2.3. Bioactivity

As mentioned before, due to its high specific area, intrinsic wrinkles and hydrophilic nature, GO shows satisfactory linkage with surrounding tissues without causing obvious toxicity to cell proliferation and tissue regeneration. Indeed, some studies have found that graphene and GO can boost some positive host responses or bio-activation.

Zhao and collaborators [129] conducted comprehensive biocompatibility studies employing MC3T3-E1 cell morphology, cytotoxicity, proliferation, differentiation and apoptosis and demonstrated that GO-coated quartz substrate is fully biocompatible with MC3T3-E1 cells. Indeed, the rapid formation of a hydroxyapatite (HA) layer in the simulated body fluid (SBF) was observed and the differentiation of MC3T3-E1 cells was enhanced by the GO coatings. This strongly indicates the bioactivity and the osteogenesis of GO-coated substrate.

Lee et al. [130] reported that GO could be an preconcentration platform to effectively accelerate the growth and osteogenic differentiation of mesenchymal stem cells (MSCs), as shown in Fig. 7. In particular, GO can enhance adipogenic differentiation due to its high affinity for insulin, an important regulator for fat synthesis. It was concluded that the π–π stacking, electrostatic interaction and hydrogen bonding caused by graphene and GO play an important role in stem

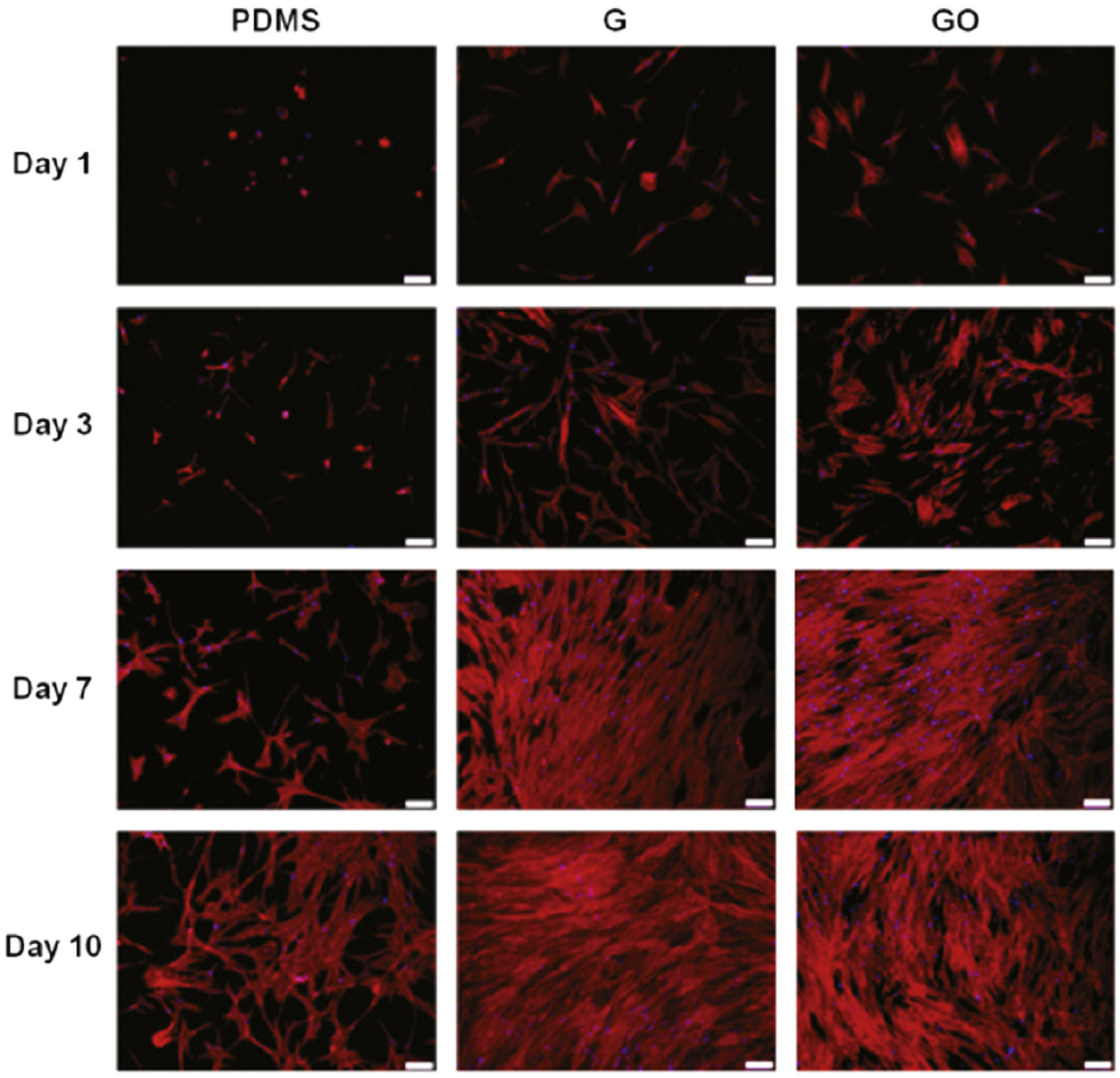

Fig. 7. Fluorescent images of proliferation (actin cytoskeleton) of MSCs cultured on PDMS, graphene and GO at day 1, 3, 7 and 10. Scale bars are 100 μm [130].

cell growth and differentiation. Likewise, Tang and co-researchers [131] found that highly cross-linked GO promoted the spontaneous stem cell differentiation towards bone without any osteogenic chemical inducers, signifying the potential of GO as a biocompatible scaffold for MSCs in tissue engineering. The nanotopography of GO contributes to the improved cell differentiation. Agarwal et al. [132] reported the excellent biocompatibility of rGO with neuroendocrine PC12 cells, oligodendroglia cells and osteoblasts. Similarly the findings were attributed to the distinct 2D nanostructure of rGO.

3.3. Antibacterial activity

Graphene-based materials especially GO and rGO have been shown to be non-toxic even at a high concentration and are hence biocompatible to mammalian cells. It is of interest to find that some graphene-based materials have antibacterial properties, which is desirable since bacterial-induced infection occurs frequently in biomaterial implantation procedures.

It has been reported that the antibacterial efficacy of graphene-based materials depends on the materials concentration, materials properties, exposure time and the type of bacteria tested. In general, bacterial viability decreases with increase of contact time and the concentration of graphene-based materials. For example, Hu et al. [133] reported that after 2 h exposure the viability of *Escherichia coli* reduced from 70% to 13% when the concentration of GO increased from 20 to 85 μg/mL; when using the same concentration of 85 μg/mL, the viability of *E. coli* was 13% and 24% respectively after exposing to GO and rGO for 2 h. In addition to GO and rGO solution, the incorporation of graphene-based materials (GO, rGO) in polymer matrixes was shown to reduce bacterial cell viability [134]. Although the antibacterial mechanism of graphene-based materials is still under study, some researchers proposed that viability decrease is associated with direct damage of bacterial membranes by the sharp edges of GO and rGO and/or by oxidative stress [134].

The potential of graphene in protecting dental implant surfaces against cariogenic *Streptococcus mutans (S. mutans)* has been explored by Kulshrestha and co-researchers [135] by evaluating the antibacterial, anti-biofilm and anti-adherence activity of graphene/zinc oxide nanocomposites (GZNC).

Their results clearly demonstrated that GZNC coated acrylic tooth surfaces successfully inhibited *S. mutans* biofilm (85%) formation. It is known that wear of artificial tenth is one of the major issues for oral tribology [136]; however, no biotribological wear tests were conducted to evaluate the wear resistance and hence the durability of the GZNC coating.

Ideal biosurfaces should prevent bacteria from growth (i.e. high antibacterial efficacy) while promoting cell attachment and proliferation (i.e. good biocompatibility). However, there is no direct correlation between these two biological features and should be evaluated for each case. For example, Santos et al. [137] observed that the addition of graphene nano particles into PVK matrix supressed biofilm formation but slightly decreased cell viability; on the other hand, however, Zhao and co-researchers [138] reported that GO modified cotton fabrics can inhibit almost completely bacteria proliferation without causing any irritation to rabbit skin even after 72 h contact.

4. Biosurface engineering with graphene

It is clear from the discussion above that graphene-based materials possess excellent mechanical and tribological properties in conjunction with good biocompatibility and attractive antibacterial properties. Hence, graphene-based materials can be potentially used to engineer biomaterials surfaces (i.e. biosurface engineering) for high-performance and long-life medical devices and body implants.

4.1. Limitations of current Implant biomaterials

Biomaterials are natural or artificial materials that are used in biological systems. Among all the biomaterials, the demand for implant materials, especially spinal, hip and knee replacements, becomes extremely high in recent years [116]. An implant biomaterial must meet several basic requirements, including biocompatibility, mechanical, tribological, corrosion properties [116,139], in order to avoid or reduce rejection and revision surgeries. The limitation of current implant materials could be demonstrated by way of example of the evolution of the design and materials for hip replacements.

The combined requirement of strength and toughness ensured the use of metallic biomaterials such as austenitic stainless steel, Co–Cr alloys and titanium alloys for the femoral components of hip prostheses. Metal-on-metal hip joints were first introduced in 1940s but very high premature failure rates were observed mainly due to high friction of metal/metal tribopair. To address this problem, Sir John Charley developed his low-friction arthroplasty consisting of polyethylene cup against stainless steel femoral head. Total joint arthroplasty based on UHMWPE/metal is widely regarded as one of the greatest achievements in the field of biomaterials and bioengineering in the last century.

However, clinical practices show that most patients currently can expect their new joints to work effectively for some 10–15 years mainly due to the wear of UHMWPE. The wear debris thus formed lead to periprosthetic osteolysis and then aseptic loosening. One approach is renewed metal-on-metal articulating surface and the other is to increase the wear resistance of UHMWPE by cross-linking. Nano-sized metal wear debris present major challenge to metal-on-metal joints whilst the wear resistance of cross-linked UHMWPE still needs to be improved further.

The second challenge to the longevity of reconstructive medical implants (such as hip and dental implants) is their long-term secure fixation in bone to restore adequate function. Bone cement (polymethyl methacrylate, PMMA) has been used for many years but it has been gradually recognised that fragments of bone cement is one of the reasons for the abrasive wear of metallic articulating surfaces. Hence, cementless fixation has gained substantial interest but due to the bio-inert nature of metals (especially Co–Cr and stainless steel), osseointegration at the tissue-implant interface is normally poor. Bioactive ceramics such as hydroxyapatite (HA) have desirable osteogenic function but both the mechanical properties and the bonding between the coating and the implant surface need to be improved [140].

The third challenge to the success of joint replacements is post-operation infection, which is a leading cause of revision operation with substantial morbidity and mortality mainly because of colonisation of pathogenic microorganisms. Hence, it is desirable for implant surfaces to have both osteogenic function and anti-bacterial activity.

4.2. Biosurface with graphene

As discussed above, friction and wear of articulating surfaces (biotribology), tissue-implant interactions and anti-bacterial activity are three major technological challenges for high-performance and long-life medical devices and reconstructive medical implants in particular. As overviewed in Sections 2 and 3, graphene-based materials possess attractive tribological properties in terms of very low friction and high wear resistance and adequate biocompatibility, unusual bioactivity and antibacterial properties. Therefore, graphene-based materials and coatings could open new horizons for addressing these three challenges. However, this is a new research field as evidenced by the limited number of related publications (see Table 2 below). This section overviews the recent development of generating novel biosurface potentially for biotribological applications based on graphene-based materials either as reinforcement or as coatings for bio-polymers (such as UHMWPE), bio-ceramics (such as HA) and metallic biomaterials (such as Ti).

4.2.1. Graphene-reinforced composites

4.2.1.1. Graphene-reinforced UHMWPE. The reinforcement of UHMWPE using graphene or graphene oxide has been studied recently by some researchers. Lahiri et al. [96] prepared UHMWPE composites reinforced with varying amount (0, 0.1, 0.5 and 1 wt%) of graphene nanoplatelet (GNP), i.e. multilayer graphene or ultrathin graphite by hot pressing. It was shown that increasing the GNP content led to decrease of the friction coefficient, due to the easy shear of

Table 2
Summary of studies on graphene modified biosurfaces for potential biotribological applications.

Material	Coating or reinforcement	Substrate or matrix	Tribological	Mechanical	Biocompatibility	Ref.
Graphene/ Calcium Silicate (CS)	C	Ti6Al4V	Higher COF and much lower wear loss (reduced from 28.6 down to 1.3 mg)	–	Osteogenesis-related gene expression of the hMSCs were higher than on Ti and pure CS coatings	[149]
GO	C	Ti/TNTZ	COF 0.16; Anti-wear life $>$10,000 s under 100 mN	–	–	[80–82]
Graphene	C	Ti6Al4V	–	Did not affect the hardness of the Ti alloy (5.63 GPa)	–	[150]
GO/HA	C	Ti	–	Enhanced adhesion; Fracture toughness improved by 280%; Improved elastic modulus (4.25 GPa), close to human skeletal bone ($\sim$10 GPa)	Proliferation of Human osteoblast cells (HFOB 1.19 SV40 transfected osteoblasts) was enhanced	[144, 145]
GO/HA	C	Ti	–	Surface cracks reduced and adhesion enhanced	Dose-dependent cytotoxicity to osteoblasts; Promoted proliferation of L969 and MG63 cells; Corrosion resistance in SBF enhanced	[93, 146]
GNP/HA	C	Ti	–	Surface cracks reduced; Hardness doubled; Elastic modulus increased by $\sim$50%	Superior biomimetic mineralization (a new apatite layer formed in SBF); No anti-bacterial effect on *S. aureus* TL and *E. coli*	[151]
GO	C	Ti	–	–	Sustained release of BMP-2 in vitro; The dual delivery of BMP-2 and SP enhanced the bone formation in mouse calvaria	[147]
GO/Na	C	Ti	–	–	Improved corrosion resistance in SBF; The viability of human dermal fibroblast cells significantly enhanced	[152]
GNP	R	TiAl	COF reduced by 4 and wear by up to 9 orders of magnitude under 10 N	A wear-induced layer and a grain refinement sub-layer formed after sliding; The hardness and elastic modulus of the latter is higher than the former	_	[101, 102]
rGO	C	316L	–	–	No toxic effect on mammalian cells (HUVECs)	[148]
GO	R Up to 3 wt%	UHMWPE	Wear rate reduced significantly by adding GO;	Hardness increased with GO content	–	[95]

			COF increased slightly with GO content;			
GO	R Up to 1 wt%	UHMWPE	–	Improved the hardness and yield strength slightly; Optimum at 0.5 wt%	Did not affect the morphology and viability of MC3T3-E1 osteoblasts	[91]
GNP	R Up to 1.0 wt%	UHMWPE	68% Lower COF; Wear resistance improved by 4 times; (1.0 wt% GNP)	Low concentration (0.1 wt%) led to most improved fracture toughness (54%) and tensile strength (71%); 1.0 wt% GNP led to improved elastic modulus and yield strength but greatly reduced tensile strength	Viability of osteoblasts decreased with GNP; By 6–16% and 86% for 0.1 wt% and 1.0 wt% GNP, respectively	[96, 141]
Graphene	R 0.5/1.0 wt%	HA	–	Fracture toughness increased by up to 80% at 1.0 wt% G; Elastic modulus and hardness by 40% and 30% respectively	Enhanced adhesion of osteoblast (MC3T3-E1) and promoted apatite mineralization in SBF	[143]
rGO	R	HA	–	Hardness up to 291 ± 36 MPa	Anti-bacterial effect on *E. coli* XL1 Blue was observed	[109]
GO/rGO	R Up to 1.5 wt%	HA	–	Elastic modulus and fracture toughness were improved by 86% and 40%, respectively with increasing rGO content	Promoted adhesion and proliferation of HFOB 1.19 SV40 transfected osteoblasts	[92]
GO	R 60 wt%	HA	–	Doubled hardness (242.06 ± 7.28 MPa) and Young's modulus (6.20 ± 1.67 MPa)	Promoted the deposition of HA in SBF; Better MC3T3-E1 osseointegration and bone cellular proliferation.	[153]
GO	C	Glass/HA	_	–	Rapid formation of HA layer in SBF; Enhanced cell differentiation of MC3T3-E1	[129]
GO/ZnO	C	Acrylic teeth	_	_	Significant reduction in biofilm and the cariogenic properties of *S. mutans;* Non-toxic to HEK-293	[135]
GO	R	Poly (acrylic acid)/ gelatin	_	Young's modulus and maximum stress significantly increased with 0.2 wt% GO	_	[154]
GO	R Up to 10%	PTFE	Wear reduction ~4000 folds	_	_	[98]

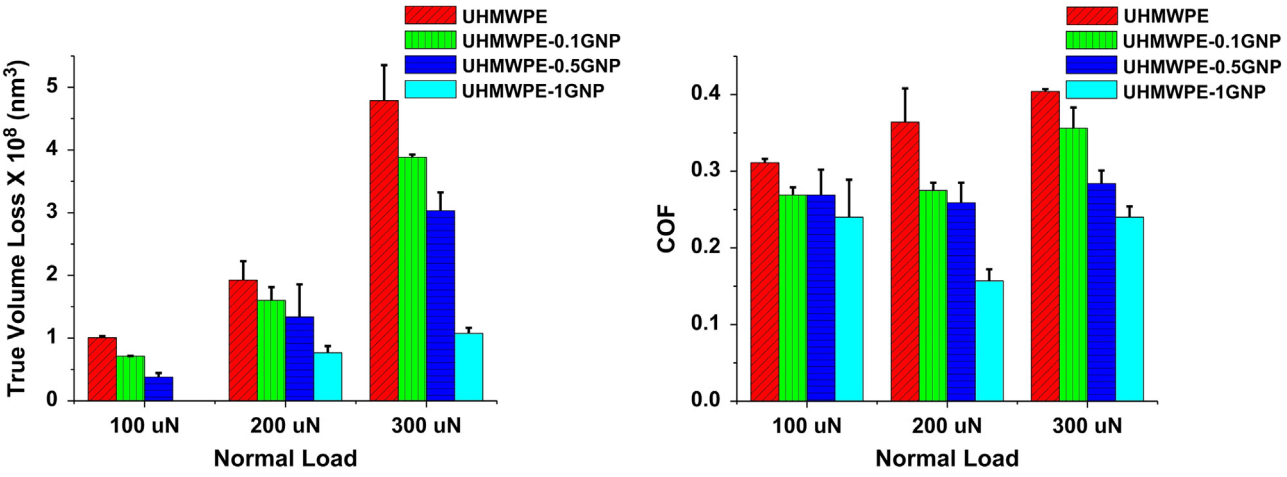

Fig. 8. Wear volume loss and coefficient of friction during scratching at different loads [96].

graphene layers, as discussed in Section 2. The wear of UHMWPE was found to decrease by 4 times due to the high in-plane strength and lubricating effect of the GNPs (Fig. 8). Similarly, Tai and co-researchers [95] investigated the addition of GO on the friction and wear of UHMWPE and found that when the content of GO was no more than 1 wt% both the hardness and wear resistance of the composites were improved. However, the friction was marginally increased by adding GO. The improvement of wear resistance of graphene-reinforced UHMWPE could be attributed to the graphene-containing transfer layer formed on the contact surface of the composite.

Lahiri et al. [141] also studied the mechanical properties and biocompatibility of the GNP/UHMWPE composites and found that the elastic modulus and yield strength of UHMWPE increased with the GNP content ranging from 0.1 to 1 wt%; at a low concentration of 0.1 wt% GNP, the composite showed a maximum improvement in fracture toughness (54%) and tensile strength (71%). The deformation mechanism was illustrated as the wrapping of polymer and the GNP-polymer interfacial strengthening.

Chen et al. [91] reported that for GO reinforced UHMWPE no obvious toxicity to MC3T3-E1 cells was observed; in contrast, however, a dose-dependent cytotoxicity was observed by Lahiri et al [141] and a low GNP content led to a high survivability of cells. The difference in toxicity observed by Lahiri et al. and Chen et al. could be related to the different chemistry of graphene nanoplatelet (GNP) and GO sheet, as discussed in Section 3.2, and the different testing protocols used by Lahiri et al. (sulforhodamine B assays) and by Chen et al. (MTT assays). Hence, it follows that reinforcement of UHMWPE with a certain amount of GNP and GO could be effective for application in acetabular cup in view of the reduced friction, enhanced wear resistance and negligible toxicity.

4.2.1.2. Graphene-reinforced hydroxyapatite. Because of its chemical and crystallographic similarity to natural apatite, hydroxyapatite (HA) has been used as bioactive calcium phosphate ceramic for bone repair or regeneration; HA coatings have also been fabricated on joint prostheses to improve the osseointegration at the bone/implant interface. However, as discussed in Section 4.1, the mechanical (especially toughness) and wear properties of pure HA need to be improved further.

Because of the high mechanical properties and low coefficient of thermal expansion, graphene has been successfully used to reinforce ceramics. Therefore, graphene-based materials (graphene, GO and rGO) can be used for the reinforcement of HA via a variety of methods including plasma sintering, HIPping, RF CVD, in-situ synthesis and electro-spinning etc. For example, compared to the pristine nano hydroxyapatite (nHA), the HIP sintered nHA/rGO composites show improvements in elastic modulus and fracture toughness by 86% and 40% respectively; the addition of the rGO promoted osteoblast adhesion and proliferation [92]. Liu et al.'s work [142] also demonstrated that compared with pure HA, the HA/rGO composites revealed significant increase in both their mechanical properties (hardness by 25.8%, elastic modulus by 47.6% and fracture toughness by 203%) and biological properties (enhanced proliferation and alkaline phosphate expression level of osteoblast cells). Similarly, improved fracture toughness (80%) and enhanced osteoblast adhesion and apatite mineralization were observed for plasma sintered 1.0 wt% graphene nanosheets (GNS)/HA composite [143].

As in UHMWPE, the cytotoxicity of the graphene-based fillers is reported to be dose-dependent. However, most of the HA matrix composites reinforced by graphene and its derivatives showed a positive biological response to the proliferation and growth of L929 fibroblast cells, MC3T3-E1 pre-osteoblast cells and MG63 human osteosarcoma cells [93].

Although there are no reports openly available on the tribological properties of graphene-reinforced hydroxyapatite, improved tribological properties and wear resistance in particular of HA could be expected by the reinforcement of graphene-based materials. This is because according to the tribology theory, the wear of ceramics mainly depends on their hardness and toughness. Hence, graphene-reinforced hydroxyapatite composites are not only a favourable bioactive ceramic for osseointegration but also a promising material for load-bearing orthopaedic implants.

4.2.2. Graphene-based coatings

Graphene-reinforced hydroxyapatite matrix composites have been coated on commercially pure (CP) Ti substrate by Liu et al. using vacuum cold spraying (VCS) [144,145] and Li et al. using electrophoretic deposition(EPD) [93,146]. Their work has revealed that the EPD deposited GO/HA composite coating outperformed pure HA and uncoated Ti in terms of reduced surface cracks, increased coating adhesion strength ($>100\%$ for 5 wt% GO/HA), better corrosion resistance in simulated body fluid and superior in vitro biocompatibility (for 2 wt% GO/HA) [93]. Likewise, Liu et al. confirmed that the VCS deposited graphene nanosheets (GN) reinforced HA coating is superior to pure HA as evidenced by better interface bonding, 4-time increase in fracture toughness and markedly enhanced attachment and proliferation of osteoblast cells [145]. The enhanced fracture toughness could be attributed to GN/GO induced interlocking or crack bridge [144,145]. In addition, GN/GO could mitigate the mismatch of thermal expansion coefficients of HA and Ti, thus enhancing the coating adhesion to the Ti substrates. However, no information on the bio-tribological behaviour of the graphene-reinforced hydroxyapatite matrix composite is reported.

La and co-researchers [147] explored the possibility of using GO-coated Ti as a vehicle for delivery of bone morphogenetic protein-2 (BMP-2), an osteoinductive protein, and Substance P (SP), a stem cell recruitment agent for in situ bone regeneration. Their work demonstrated that the dual delivery of BMP-2 and SP using GO-coated Ti showed the greatest new bone formation on Ti implanted in the mouse calvaria (Fig. 9). Hence, Ti implants coated with GO could be an approach to improve osseointegration of dental and orthopaedic implants.

Li et al. [80–82] fabricated GO and rGO coatings on Ti–29Nb–13Ta–4.6Zr (TNTZ) alloy via self-assembling as described in [74]. It was shown that the ultra-thin (3.3 nm), self-assembled GO coating effectively improved the tribological properties of TNTZ in terms of largely reduced adhesion force, a low friction coefficient of 0.16 and an anti-wear life of more than 10,000 s. A bio-tribological test was conducted by immersing the GO coated Ti alloy in 0.15 M sodium chloride solution for 30 days before tribological testing. The results suggest the same friction coefficient and an anti-wear life of 5300 s.

316L austenitic stainless steel surfaces were also coated by reduced graphene oxide (rGO) coating synthesized from coronene by solution deposition (i.e. drop casting) and annealing in a gas mixture of 98% nitrogen and 2% hydrogen at temperatures between 600 and 800 °C for 30 min. It was revealed that the rGO surface layer improved the wettability of 316L and the rGO coated 316L is nontoxic to mammalian cells [148].

It has also been reported [135] that graphene/zinc oxide nanocomposite (GZNC) can be used as a coating material to effectively protect artificial acrylic teeth surfaces from the formation of oral biofilms, which is one of the major causes of dental implant failure. As shown Fig. 10, the un-coated artificial acrylic teeth (control) depicts well-defined biofilm architecture (a, b and c) whilst the treated surface showed almost negligible biofilm (d, e and f).

Xie et al. [149] fabricated graphene/calcium silicate (CS) composite coatings on Ti–6Al–4V substrates by a vacuum plasma-spraying technique and studied the tribological properties of the graphene/CS coated Ti–6Al–4V. The results confirmed the homogeneous embedment of graphene plates and a hierarchical hybrid nano-/microstructured surface. It was found that the wear decreased with the increasing graphene content. The incorporation of 1.5 wt% graphene reduced the weight loss dramatically from 28.6 ± 0.5 to 1.3 ± 0.2 mg. However a content of more than 4% led to porous coatings and increased wear. The *in* vitro experiment on human marrow stem cells (hMSCs) showed that graphene exhibited no toxicity to the proliferation of the cells; instead it even enhanced the adhesion, which was attributed to the unique nano-microstructure of the composite coating. Their results are in great agreement with the studies on wear behaviour of graphene-based composite coating [86] and bioactivity of graphene [131,132], indicating successful biotribological application of graphene.

5. Summary and concluding remarks

5.1. Summary and conclusions

Due to its astonishing physical and mechanical properties, graphene has received extensive scientific interest since pristine graphene was isolated in 2004. Recently, the promising tribological and biomedical properties of graphene and its derivatives (mainly GO and rGO) have attracted great attention of tribologists and biomedical researchers.

Graphene possesses a low friction and high lubricity provided they are strongly bonded to smooth substrates. Doping of graphene will increase its friction and the friction increases in the order of graphene, rGO and GO. Graphene-based coatings can effectively reduce wear and friction of steel and silicon wafers, and GO has been successfully used to reinforce polymers to form GO/polymer composite coatings to effectively improve the wear of polymers. Due to their unique structure and properties graphene and its derivatives (mainly GO and rGO) have shown strong bioactivity and high anti-bacterial efficacy although there exist some concerns over their long-term cytotoxicity. Among graphene and its derivatives, graphene oxide is superior to pristine graphene in terms of biocompatibility, bioactivity and anti-bacterial efficacy mainly due to its hydrophilic nature.

Graphene and its derivatives can effective increase the mechanical (strength, toughness and hardness) and tribological (wear and lubrication) properties of biopolymers (such as UHMWPE) and bioceramics (such as HA). Although the cytotoxicity of these graphene-reinforced bio-composites is dose-dependent, in general they have a positive biological response to the proliferation and growth of many biological cells. Graphene-based coatings have been applied to commercially pure Ti, Ti–29Nb–13Ta–4.6Zr and Ti–6Al–4V alloys, 316L stainless steel and artificial acrylic teeth surfaces, and *in* vitro test results have shown some preliminary promising results. GO-coated Ti has been successfully used to deliver

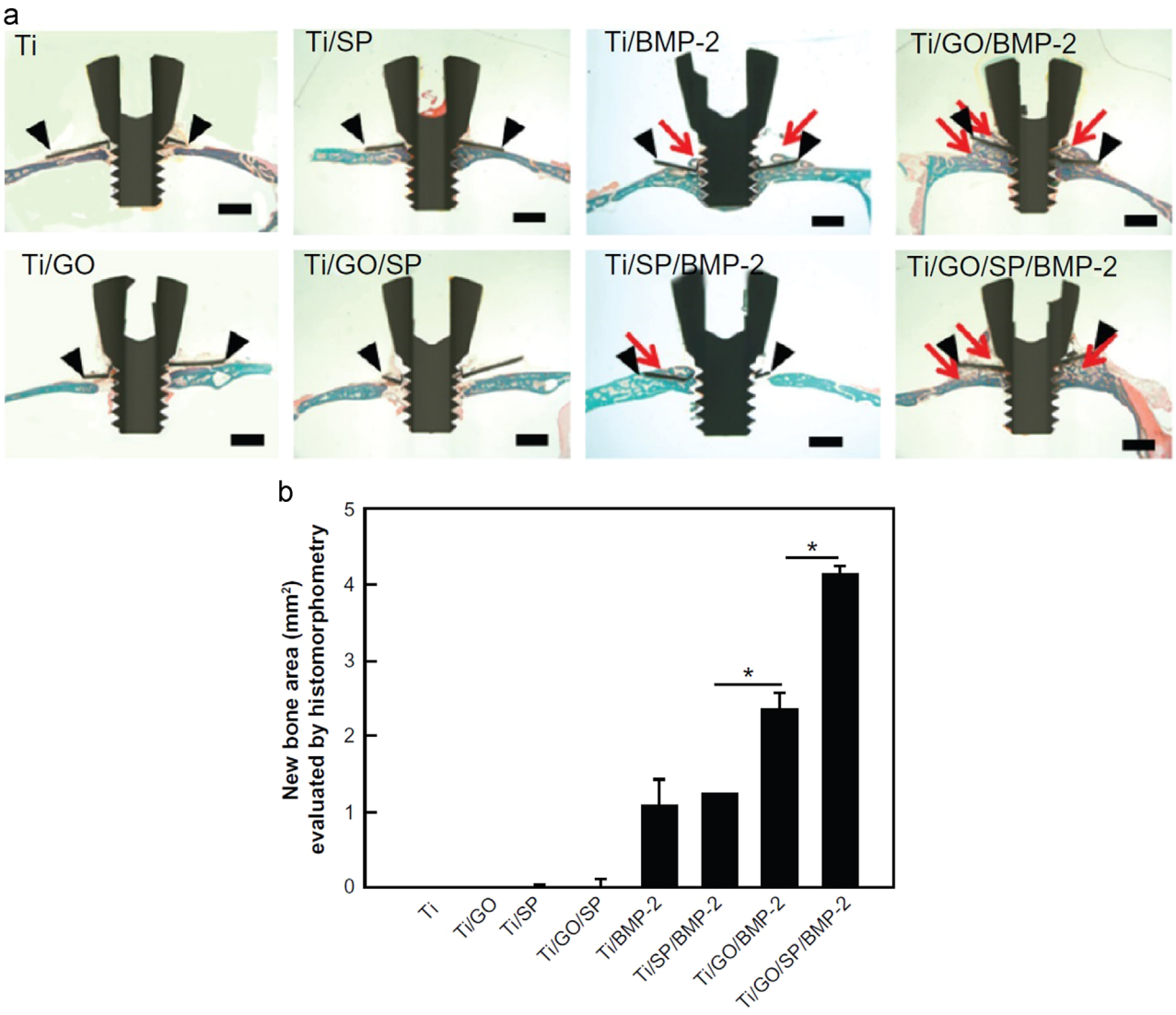

Fig. 9. Bone regeneration of Ti ring implants with or without GO coating, BMP-2 (bone morphogenetic protein-2) and SP (substance P) loading in mouse calvarial defect model. (a) (× 12.5) images of the implants. The black and red arrows indicate the implant and newly formed bone, respectively. Scale bars = 1 mm. (b) The area of new bone formation was determined using histomorphometric analysis ($n = 5$). *$P < 0.05$ between designated two groups [147].

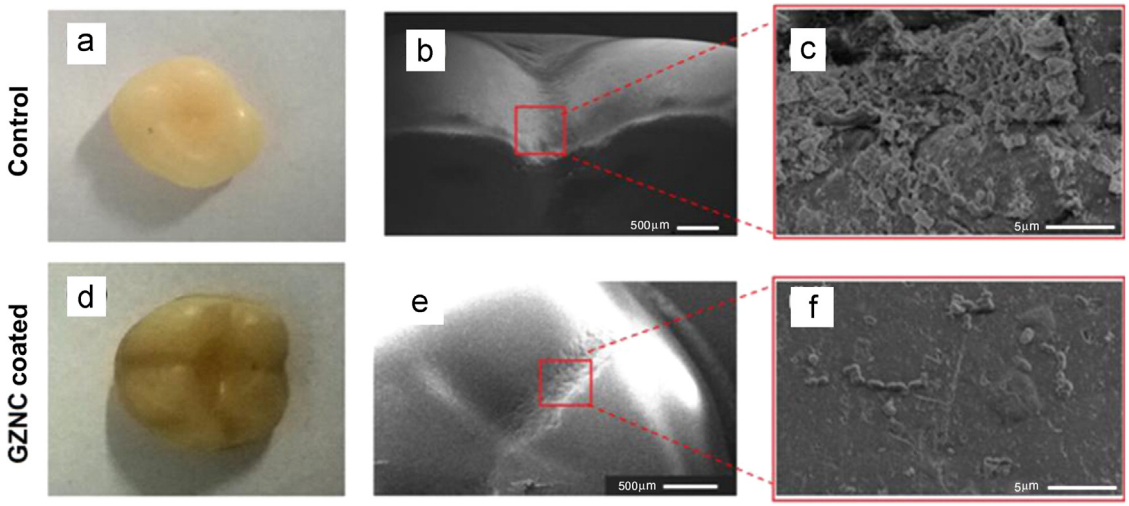

Fig. 10. Photographs of (a) non-coated and (d) GZNC coated acrylic teeth. SEM analysis for biofilm formation on non-coated (b and c) which shows well-defined biofilm architecture and GZNC coated (e and f) teeth showing almost negligible biofilm [135].

osteoinductive and stem cell recruitment agent for in situ bone generation on Ti implanted in the mouse calvaria; graphene/zinc oxide nanocomposites coating can be used to effectively protect artificial acrylic surfaces from the formation of oral biofilms.

Clearly, graphene and its derivatives and GO reinforced composites could be ideal low-friction, self-lubricating, bioactive and anti-bacterial materials for biosurfaces.

5.2. Future directions

Notwithstanding the fact that graphene-based materials have shown attractive mechanical, tribological and biological properties, their full potential for high-performance and long-lasting biosurfaces will not be realised until the following scientific challenges and technological barriers are addressed, which forms the future directions.

The first direction is the fundamental research to advance scientific understanding on the long-term biocompatibility and potential toxicity in particular of graphene-based nanomaterials and coatings as a function of their geometry (size and shape), chemistry (dopants and amount) and the percentage of graphene-based materials in composites. The second is the development of advanced surface engineering technologies to deposit large-area coatings of graphene-based materials (graphene, rGO and GO) [155] and their nanocomposites on biomaterials and medical device surfaces with sufficient bonding strength and durability. The third is in-vitro biotribological tests of engineered biomaterials surface (i.e. biosurfaces) with graphene-based materials and graphene reinforced nanocomposite coatings. The fourth is in-vivo trials of graphene surface engineered implants with outstanding tribological properties and acceptable biocompatibility in conjunction with desirable bioactivity or high anti-bacterial efficacy for orthopaedic, orthodontic and cardiovascular applications.

Acknowledgement

The authors would like to thank Professor Z.R. Zhou of Southwest Jiaotong University for his encouragement and one of the authors (SQ) wishes to express his appreciation to China Scholarship Council (CSC) and The University of Birmingham for the PhD studentship.

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